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An Epidemiological Approach to Depression Prevention in Old Age

Filip Smits, Ph.D., Niels Smits, Ph.D., Robert Schoevers, M.D., Ph.D., Dorly Deeg, Ph.D., Aartjan Beekman, MD, Ph.D., Pim Cuijpers, Ph.D.

Objective: *To identify target groups for prevention of chronic or recurrent depression in old age such that prevention is likely to become cost-effective.* **Methods:** *Data were used from a population-based cohort study (N = 2,200). Chronic or recurrent depression was defined when people presented with clinically high levels of depression at two time points separated by 3 years. Risk profiles of these conditions were identified using classification and regression trees analysis. The combinations of risk factors were then evaluated in multivariate models to ascertain their utility for preventing depression in high-risk groups.* **Results:** *People are placed at a high risk of depression when having symptoms of anxiety, functional impairments, two or more chronic illnesses, and either a low attained educational level or below average levels of mastery, while living without a partner. These risk profiles correspond with groups no larger than 8.3% of the older population. Containing the adverse effects of the risk factors would help to reduce the incidence of depression by possibly as much as 48.7%, indicating that large health gains can be generated, which can also be done efficiently with numbers-needed-to-be-treated, perhaps as small as three.* **Conclusion:** *Targeting prevention on the selected high-risk groups is likely to become a cost-effective endeavor, because optimal health gains can be generated efficiently in groups small enough to be logistically manageable. The burden of illness associated with depression, particularly depression, in aging populations underscores the public health significance of such an approach.*(Am J Geriatr Psychiatry 2008; 16:444–453)

Key Words: Prevention, depression, target groups

Late-life depression has a great public health significance due to both its high prevalence and the amount of disability it causes.[1] For the year 2020, depressive disorder is projected to be the second

Received October 15, 2007; revised November 26, 2007; accepted December 10, 2007. From the Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Utrecht (FS); Department of Clinical Psychology (FS, NS, PC), VU University; Department of Psychiatry (DD, AB), Institute of Extra-Mural Medicine (EMGO) (FS, NS, DD, AB, PC), VU University medical centre, VU University, Amsterdam; Community Mental Health Centre JellinekMentrum, Amsterdam (RS); and Community Mental Health Centre Buiten-Amstel, Amsterdam (AB). Send correspondence and reprint requests to Filip Smit, Ph.D., Trimbos Institute, Centre of Prevention and Early Intervention, P.O. Box 725, 4500 AS Utrecht, the Netherlands. e-mail: fsmit@trimbos.nl

leading cause of disease burden, ranking only under ischemic heart disease.[2] Moreover, propelled by the demographic transition in most Western countries this burden will progressively shift toward the older age groups. Late-life depression is further associated with excessive health care uptake[3,4] and economic costs.[5,6] This should place late-life depression in the limelight of interest of the public health planners.[7]

Although effective treatments are available for depression[8,9] they can only partially alleviate the disease burden at the population level. Bottlenecks are budgetary constraints and limited availability of qualified therapists, even in high-income countries. Moreover, not all depressed people solicit professional help or will be identified as depressed, whereas those identified may not receive evidence-based treatment. As a result, the maximum health gain attributable to treatment has been estimated to be around 30%.[10,11] Another important issue is the enormous annual influx of new cases of depression: one in every five cases of clinically relevant late-life depression is, in fact, a new or recurrent case.[12] For these reasons it is crucial not to solely rely on treatment, but also to attempt to reduce the number of new cases. For that prevention is needed.

In this context it is important to note that prevention can be effective.[13] A meta-analysis of randomized trials demonstrated that psychological interventions can reduce the incidence of full-blown depressive disorders by 30%.[14] Although encouraging, it is not immediately clear to whom preventive interventions are best directed. After all, even in later life spontaneous remission occurs in 23% of new cases,[15–17] and one would like to target preventive interventions on the other 77% where depression is likely to persist when no intervention is offered.

Here we take an epidemiological approach and look for clinical and social demographic factors predictive of depression that may be used to identify groups in which prevention is likely to be most successful. To that end, we want to go beyond mere identification of risk factors, and specifically identify risk indicators associated with large potential health gains. In addition, we want to select risk indicators associated with small target groups such that prevention is likely to become logistically manageable and economically affordable. In short, we want to identify target groups where preventing depression stands the best chance of becoming cost-effective.

In earlier studies[12,18,19] we showed that people in the age bracket of 55–85 years with some depressive symptoms not meeting the diagnostic criteria of depressive disorder are at a high risk of developing the full-blown disorder, especially women, and significantly more so when they have, in addition, two or more chronic illnesses or present with self-reported ill-health, feel they have only a limited amount of control over their own lives (i.e., low mastery), experience functional impairments, have attained only a low level of education, are widowed, or have a small social network. Target groups with these risk-profiles are numerically small, but account for the vast majority of new cases of depression in the population. Targeting people with these risk profiles make prevention at once manageable, economically feasible and is likely to result in relatively large health gains at population level. In the present study we will make yet another step and investigate whether the risk profile for the onset of depression is the same or different, from the risk profile for the onset of chronic or recurrent depression in late life. This would yield a more relevant risk profile for identifying target groups for prevention.

METHODS

Subjects and Procedures

The analyses were based on the data of the first two waves of the Longitudinal Aging Study Amsterdam. The sampling and procedures of this study have been described elsewhere in detail.[15] At baseline, 3,056 community residents in the age group of 55–85 years were interviewed. Participants were requested to give their informed consent and were then interviewed face-to-face in their homes. The random sample was stratified by age and gender. The older age strata and men were oversampled in anticipation of higher attrition rates among these groups during the course of the study. After 3 years (M = 1,115 days, SD: 59) 2,200 subjects (72%) were successfully reinterviewed. Loss-to-follow-up had occurred among 856 subjects, mainly because the subjects were too ill or were no longer alive at the time of the first follow-up. Predictors of loss-to-follow-up were older age, male gender, lower educa-

tion, functional limitations, chronic diseases, and cognitive decline, but not depression status at baseline.[15] Corrective weights were used to account for the joint effect of intentional oversampling and accidental attrition (see Analysis section).

Chronic or Recurrent Depression

Depression was ascertained with the Center of Epidemiological Studies Depression Scale. (Radloff, 1977).[20] It consists of 20 items and its total score has a range between 0 and 60. Scores ≥16 indicate clinically significant levels of depressive symptoms.[21] At this cutoff the sensitivity is 100% and the specificity is 88% for major depressive disorders in the elderly Dutch population.[22] Measurements were taken at baseline (t_0) and 3 years later at follow-up (t_1). A person was deemed to be a case of chronic or recurrent depression when the person scored higher than the cutoff at both t_0 and t_1. This could imply that the person was depressed all the time (chronic depression). This could also mean that a person happened to be depressed at both time points, but may have gone into remission or obtained recovery between those time points (recurrent depression). Because we are conducting secondary analysis of existing data, we have no way of ascertaining what happened exactly, but both chronic depression and recurrent depression have great clinical and public health significance.

Comparison Group

The group which is ultimately identified as having chronic or recurrent depression is compared with all the other people in the population. This choice has consequences and we will return to this in the Conclusion. Here it suffices that our choice is justified by the aim of our study: to be able to identify groups that are placed at a high risk of becoming cases of chronic or recurrent depression in the general population. This corresponds to the public health perspective taken here.

Risk Indicators

Following the vulnerability-stress theory[23] and a review on risk indicators of late-life depression[24] and our previous studies on risk profiles of the onset of depression (not chronic or recurrent depression per se),[12,18,19] the following putative risk indicators were included.

Demographics: female gender (1 = female, 0 = male), age over 65 years, that is the age at which 30% of the sample makes a significant transition in their life due to retirement (1 = older than 65 years, 0 = younger), low education (dichotomized into 1 = elementary school, 0 = high school and higher), living in an urban environment (1 = urban, 0 = not urban).

Anxiety at t_0 as measured with the Hospital Anxiety and Depression Scale,[25] the anxiety subscale (HADS-A) which was dichotomized at the cutoff score of ≥8.[26] We refer to higher scores as "anxiety."

Chronic illnesses[27] (dichotomized, 1 = two or more, 0 = one or none illnesses) among them, diabetes mellitus, chronic obstructive lung disease, cardiac disease, arthritis of knee or hip, and cancer. Earlier studies have indicated that it is not so much the presence of chronic medical conditions that predict the onset of depression, but rather the functional limitations that may stem from them, and the degree by which one's sense of mastery (locus of control) is affected.[20–30] Therefore, the following measures were also included: functional limitations[31] (1 = one or more, 0 = none) and low mastery[32] (1 = score below the 50th percentile on the scale, 0 = above 50th percentile).

Finally, social vulnerability was assessed by two additional measures: small social network (1 = below, 0 = above the median social network size of 13 people) and widowhood (1 = ever widowed, 0 = other).

All risk indicators were measured at t_0 and were coded 1 as the index category for the (presumably) elevated risk status and 0 for the reference category. Dichotomization was carried out before the analysis.

Analysis

We used classification and regression trees (CART) analysis[33,34] to derive multivariate risk profiles of chronic or recurrent depression. Conceptually, CART analysis makes combinations of risk indicators and then evaluates their cumulative effect in terms of their joint predictive power (sensitivity and specificity) with respect to the outcome of interest (depression). This is done by making tree-like diagrams (Fig. 1). At the top of the dendrogram one

finds the risk indicator that best predicts outcome. This risk indicator is called the "parental node." The parental node branches off in two directions: to the right when the risk is present (labeled yes) and to the left when the risk is absent (labeled no). So called "child nodes" appear below the parental branches. These are risk indicators that help to optimize the prediction after the effect of the parental node is taken into account. This process is then repeated for several "generations" of child nodes. At the bottom end of the branches are "terminal nodes." CART diagrams that have branches across several generations may become cluttered and not all terminal branches yield good predictive values. Therefore some selection of branches is needed. Here we can extend the botanical metaphor: branches that are successful in predicting the outcome are grafted, whereas branches that end in unsuccessful terminal nodes are pruned. This helps to avoid cluttering. Another way to avoid cluttering is to restrict to number of risk indicators in the CART analysis or, alternatively, to put a cap on the number of generations. We return to this issue later. CART diagrams were created using the statistical software package R,[35] and the optimal CART tree was automatically selected by a 10-fold cross-validation. The latter is important, because this is not a hypothesis-driven, but an explorative (data-driven) form of analysis.

Once the CART diagram was obtained, we evaluated each node in terms of statistics that interested us most. These statistics were obtained using the Stata/SE (8.2) statistical package.[36] The subsequent analyses took into account that the data were generated by a sampling design with intentional oversampling of the male and older age strata and loss-to-follow-up. Therefore, we weighted the data such that the multivariate distribution over gender and age in the sample was exactly the same as in the general Dutch population in the age range of 55–85 years as reported by Statistics, the Netherlands. In order to obtain correct 95% confidence intervals and p values under weighting, all variance-related statistics were obtained with help of the first-order Taylor-series linearization method as implemented in Stata. Weighted statistics are reported throughout the remainder of this article.

The Incidence Rate Ratio (IRR) was obtained by regressing the outcome (1 = case of depression, 0 = not a case) on each node (parental risk indicator, or on an indicator representing a combination of parental and child risk indicators) in a Poisson regression model. The IRR describes how much larger the incidence rate is in the exposed group relative to the incidence rate in the unexposed group. The IRRs were based on person-time data to account for the small differences in follow-up time between t_0 and t_1 across the subjects. IRRs larger than 1 signify an increased risk level in the exposed group.

A maximum-likelihood estimate of the population Attributable Fraction (AF) was obtained with the Aflogit-procedure in Stata for each of the risk indicators under the above Poisson model.[37] When converted into a percentage, the AF denotes by how many percent points the current incidence rate of depression in the population would be reduced if the adverse effect of the risk indicator is completely blocked.[38,39] This equals the maximum possible impact of a completely successful preventive intervention. Because it cannot be realistically assumed that preventive interventions are completely successful in containing the adverse effects of the risk indicators, it follows that the AF-statistic represents the upper limit to the potential health gain in the population. Although it is possible to adjust the AF-statistic for interventions that are not completely effective,[40] it is readily understood that we need not correct the AF-statistic for the purpose of this article: a measure of relative performance is good enough for ranking risk indicators by their utility for prevention. We will return to the interpretation of the AF later.

The Exposure Rate (ER) of each risk indicator was calculated on the basis of the weighted data. The ER gives the percentage of the elderly population exposed to the risk indicator, or set of risk indicators as they occur in a CART branch.

Finally, the number-needed-to-be-treated (NNT) of each risk indicator or set of risk indicators was calculated as the inverse of the risk difference. The latter was obtained by regressing the outcome on a risk indicator in a linear probability model, e.g., a generalized linear model with a binomial distribution for its outcome and identity as its link function. The NNT denotes how many people should receive a preventive intervention in order to avoid one new case of depression. Again, we do not expect that preventive interventions are completely successful and it is thus understood that the NNT represents the lower limit of the effort that is required to generate a health gain in the population.

To summarize, we obtained estimates of the size of the target population (ER), the strength of association between the set of risk indicators and outcome (IRR), the maximum achievable health gain (AF), and the minimum effort to generate that health gain (NNT). Together these indices of impact and effort allow us to select high-risk groups for which depression prevention is likely to be associated with the highest health benefit in the population for the lowest cost.

Finally, when the economical costs of late-life depression are known, then the cost figures can be combined with the AF. This gives an indication of the dollar value of the economic cost offsets of a future preventive intervention. The method of this ante-hoc health-economical evaluation is straightforward, but best illustrated with real data. We present such a calculation in the Discussion to high-light the implications of our findings.

RESULTS

Sample

Of the sample (N = 2,200) 53.5% were women, the age range was between 55 and 85 years, of whom 20.5% were older than 65, 37.9% had no formal education or had completed elementary school. About a quarter (26.3%) lived in highly urbanized environments, 47.3% had a social net work smaller than 13 people, 21.6% were widowed, and 27.8% lived without a partner. In clinical terms the sample can be described as follows: 8.3% had a HADS-A score above the cutoff indicating presence of clinically relevant levels of anxiety, 20.5% had two or more chronic illnesses, 14.4% made mention of impaired functioning, and 57.8% had a below-average sense of mastery (internal locus of control).

Depression Rates

It is worth noting that 12.5% of the sample had clinically relevant levels of depression at baseline, whereas 6.1% was depressed at both t_0 and 3 years later t_1. This suggests that nearly half (48.8%) the population was still depressed or experienced a recurrence of depression after 3 years. Chronic or recurrent depression is more common in women (8.2%) than in men (3.7%).

ER, IRR, AF, and NNT Statistics for the Risk Indicators

Table 1 presents for each of the risk indicators the ER, the IRR, the AF, and the numbers needed to be

TABLE 1. Exposure Rates (ER, %), Bivariate Incidence Rate Ratios (IRR), Bivariate Attributable Fractions (AF) and Bivariate Number Needed to be Treated (NNT) of the Risk Indicators Along With Their 95% Confidence Intervals (95% CI), Weighted Analysis (n = 2,200)

	ER (%)	IRR	95% CI[a]	AF (%)	95% CI	NNT
Demographics						
Female	53.5	2.26	1.53–3.33	40.0	21.0–54.5	21.8
Age over 65	20.5	2.19	1.59–3.03	26.3	14.2–36.7	17.2
Low educat	37.9	1.56	1.33–2.60	25.4	10.7–37.7	25.4
Widowed	21.6	2.19	1.57–3.04	22.7	11.6–32.4	17.3
No partner	27.9	2.67	192–3.71	34.0	21.4–44.6	14.4
Small net	47.3	1.82	1.26–2.63	28.7	10.4–43.3	29.8
Highly urban	26.3	1.99	1.42–2.77	21.1	9.4–31.3	21.1
Clinical						
Anxious	8.3	12.73	9.20–17.60	48.7	39.6–56.4	2.9
≥2 illnesses	20.5	2.92	2.10–4.06	30.0	19.0–39.5	12.0
Impaired	14.4	4.70	3.40–6.48	38.3	28.3–47.0	6.8
Low mastery	57.8	2.38	1.89–2.99	46.9	36.4–55.7	12.7

[a]Significant at $p < 0.001$; p values were obtained under the weighted person-time based Poisson regression models with robust estimates of the standard error of the estimates. The latter were computed using the first-order Taylor-series linearization method, as implemented in Stata. The test-statistic was *z*.

treated. The statistics are based on bivariate analyses and show how each of the risk indicators impacts on outcome. To illustrate, antecedent anxiety is associated with an IRR of 12.7, indicating a more than 12-fold increase in the risk of becoming a case of persisting depression conditional on exposure to t_0 anxiety. Thus we have selected a high-risk group. The AF value of 48.7% indicates that were we able to successfully treat all cases of anxiety, then the incidence of persisting depression would be almost halved. This health gain could be achieved by targeting 8.3% of the population in the age bracket of 55–85 years (ER = 8.3), which may represent, logistically speaking, not too large an obstacle. Should the intervention be completely successful in containing the adverse effects of anxiety on persisting depression, then this intervention would be very efficient in avoiding onsets of depression as one persisting depression would be avoided in every three recipients of that intervention (NNT = 2.9).

CART Dendrogram

Figure 1 presents the CART dendrogram. As can be seen, the parental node (presence of anxiety at t_0) branches off to the right-hand side and immediately ends in a terminal node, that contains the ER, IRR, AF, and NNT statistics just described. Clearly, t_0 anxiety is a risk indicator that yields the best statistics overall. The remainder of the dendrogram can be described as follows. People who have a risk profile of no anxiety, functional impairment, chronic illnesses, and low attained education have more than a threefold risk of becoming cases of chronic or recurrent depression (IRR = 3.5), blocking the adverse effects of the joint exposure to this set of risk factors will help to avoid the onset of persisting depression in 9% of the older population (AF = 9.0). To achieve this health gain only 3% of the older population has to be targeted by prevention (ER = 3.0), and the intervention can be delivered efficiently (NNT = 7.6). A final terminal node can be found at the bottom of the diagram. The corresponding risk profile is no anxiety, functional impairment, no chronic illnesses, low mastery, and no partner. It should finally be observed that some left-hand branches have been pruned, because they did not reach a terminal node that had any predictive value for the outcome.

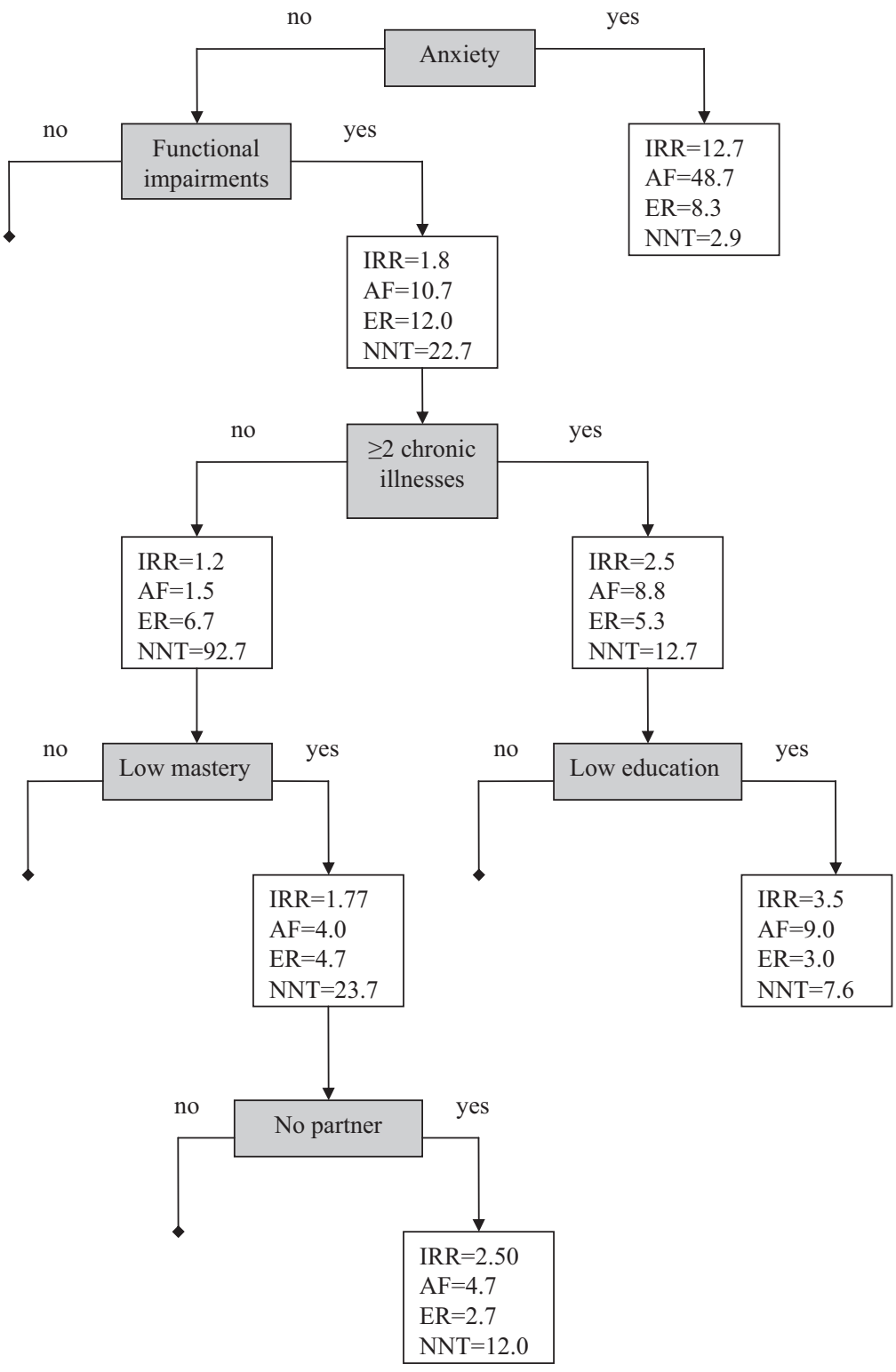
Several additional observations can be made. When we follow the dendrogram's branch from functional impairments toward the terminal node under low education then it can be seen that in each consecutive step the relative risk of becoming a case of persisting depression increases (from IRR = 1.8 to 2.5, to 3.5), indicating that accumulation of exposures is associated with an increase in the relative risk. Likewise the size of the target group gets progressively smaller (from 12.0% to 5.3% to 3.0%) and also the NNT falls sharply from 22.7 to a final 7.6. This suggests that when prevention is directed at a group with this risk profile, then preventive interventions stand a good chance of becoming efficient. It should also be observed that one of the key-parameters, the AF, gets smaller when more risk factors are stacked. This is unfortunate, because one would like to have the AF (as an indicator of potential health gain) to be as large as possible. Nevertheless, when target groups get smaller, it gets harder to generate substantial health gains at the level of the whole population. Hence there is a trade off between effort (related to the size of the target population) and benefit (the population health gain). Seen from this perspective one would perhaps regard the first terminal node (under anxiety) as optimal, because it combines a very large potential health gain (AF = 48.7) while targeting only 8.3% of the older population. It achieves this result because this relatively small target group is an ultra-high-risk group (IRR = 12.7), responsible for the bulk of new cases of chronic or recurrent depression. In this respect, the other risk profiles are perhaps best seen as "next best " options for targeting prevention.

DISCUSSION

Main Findings

In the older population as many as 6.1% presents with chronic or recurrent depression. Three sets of risk factors seem to place people at markedly elevated risk levels 1) people who suffer from HADS-A anxiety, 2) people not suffering from anxiety but presenting with functional impairments, having two or more chronic illnesses and a low educational status, and 3) people with a risk profile of no anxiety and no chronic illnesses, but with functional impairments, a below average sense of mastery, and who live without a partner. People meeting the criteria for

FIGURE 1. Dendogram of Risk Factors for Depression in Old Age



these risk profiles tend to form relatively small groups in the population (no larger than 8.3%), but account for the bulk of new cases of persisting depression. It is therefore understood that targeting these groups with preventive interventions may offer opportunities for cost-effective prevention.

Limitations

The findings have to be placed in the context of the strengths and limitations of this study. The strengths are the use of population-based data, the prospective design which strengthens etiological inference, and the measurement of exposures which is not biased due to post-hoc rationalization on the part of the respondents, because at t_0 they could not have any knowledge about their future health state at t_1. Furthermore, this study supplies the sort of methodology which is of importance for setting a rational Research and Development agenda for depression prevention.

The limitations of this study consist of the not very detailed measurement of the exposures. We do not know for how long and how intensely subjects were exposed. Moreover, the number of studied risk indicators is limited in that, for example, hereditary risk factors were not included. Another limitation is the measurement of depression with the Center of Epidemiological Studies Depression Scale, which is not a diagnostic instrument although it has good psychometrical properties. Also, we do not know if the people were chronically depressed, or experienced relapses or recurrences in the time interval of 3 years, but their respective etiology and corresponding risk factors may differ. It should further be observed that people who are exposed to several risk factors may form a population segment unresponsive to health oriented interventions and this may limit the health gain that can be delivered by prevention. This is an important issue, which needs more research.

The risk indicators found here for chronic or recurrent depression are not markedly different from those that were previously found for onset of late-life depression in general.[12,15,16,18,19] This may attest to the robustness of our findings, but also indicates that the studied risk indicators are generic risk factors rather than specific risk factors for chronic or recurrent depression. Identification of specific risk indicators would require a study design where single episodes of depression are compared with recurrent depression (to the exclusion of all other groups in the general population), rather than trying to identify groups at risk of chronic or recurrent depression from the general population, which was the principal aim of this study.

Our finding that anxiety is a strong antecedent predictor of chronic or recurrent depression is not totally surprising considering the substantial comorbidity between depressions and anxiety disorders. Still, a current anxiety disorder may flag up that people are at risk of chronic or recurrent depression, which lends our finding public health significance.

Conceptually, it would be useful to distinguish between risk indicators that are amenable, such as anxiety symptoms, from those that are not. It is also worth noting that some risk indicators are not modifiable, like chronic illnesses, but their adverse psychological effects might be contained. Finally, there are risk indicators, such as female gender, which are not modifiable, but are valuable from the perspective of identifying groups at risk—which was the principal aim of this article.

Health Economic Implications

Avoiding onsets of chronic or recurrent depression has economic ramifications. In the United States the costs of depression are conservatively estimated at US$ 2,090 per depressed person per year.[5] We base our calculations on a source population of 1 million people aged 55–85 years. In this population we expect to see 6.1% to be chronic or recurrent depressed over a period of 3 years. This would entail 1,000,000 × 0.061 × 3 years × US$ 2,090 = US$ 382,470,000 in costs over 3 years attributable to only the chronically or recurrent depressed cases. This figure becomes less when not all 3 years are spent in a chronically depressed condition. Assuming that not all 3 years but a single year is spent in a clinically depressed mood we would arrive at a figure of US$ 127,490,000 due to chronic or recurrent depression in a source population of 1 million.

As has been shown, providing effective treatment for anxiety would help to reduce the number of cases by almost one half (AF = 48.7%). This would thus help to avoid 1,000,000 × 0.061 × 0.487 = 29,707 onsets, resulting in cost savings equivalent to 29,707 × US$ 2,090 = US$ 62,087,630 assuming that

people would otherwise have spent 1 year (not the whole 3 years) in this condition. It is unrealistic to assume that the intervention directed at anxiety would be completely successful, but anxiety is an amenable condition, and if the intervention would be successful in 60% of the anxiety cases, this still would amount to an economic saving of US$ 3,725,2578 that otherwise would have been generated by higher rates of depression in the source population.

We have to address one final issue: offering the intervention would entail some costs of its own. As noted before, the intervention should be offered to 8.3% of the older population, i.e., to 83,000 people. Hence, the per-patient costs of the intervention may be as large as US$ 3,725,2578/83,000 = US$ 449 before we reach the break-even point where the investments in the intervention are just balanced by the cost offsets. A web-based self-help therapy for anxiety, possibly enhanced by minimal therapist contact, may fit these parameters, and thus help people not only to overcome their anxiety, but also to prevent the onset of chronic or recurrent depression in a fairly large segment of the older population in a cost-effective way.

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